

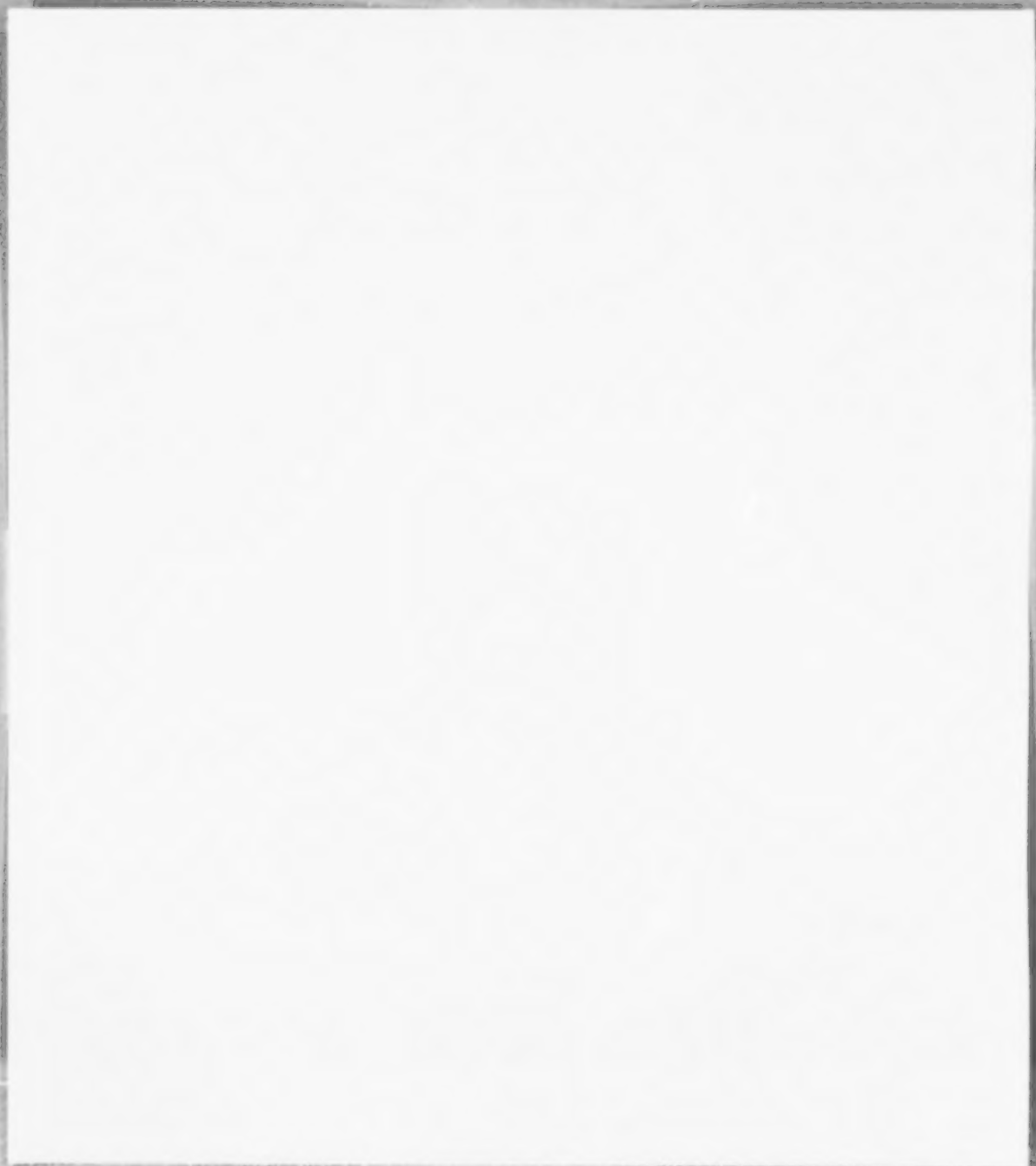
WORLD



THE MAGAZINE OF THE WORLD HEALTH ORGANIZATION

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WORLD HEALTH

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Editorial

Tuberculosis: a global emergency

Tuberculosis currently kills three million people a year. Unless immediate action is taken it will claim more than 30 million lives during the coming decade. The disease is out of control in many parts of the world.

Tuberculosis is the leading cause of death from a single infectious disease, accounting for over a quarter of avoidable deaths among adults. The great majority of cases, and more than 95% of deaths, occur in the developing world. However, the number of cases in Europe and North America has risen dramatically in the past five years. The disease cannot be controlled in the industrialized countries unless it is sharply reduced as a health threat in the developing countries of Asia, Africa and Latin America.

Infecting eight million new victims a year, tuberculosis also has a deadly link with AIDS. People infected with both HIV and the tuberculosis bacillus have a 25-fold increased risk of developing potentially fatal disease.

Cost-effective tools exist for

The WHO Tuberculosis Programme's current objectives

- Reducing the death rate from tuberculosis – currently 3 million people per year – by half by the year 2000.
- Cutting transmission and infection rates of the disease by identifying and supervising the treatment of infected persons until they are completely cured.

Tuberculosis cannot be controlled in the industrialized countries unless it is sharply reduced as a health threat in the developing countries of Asia, Africa and Latin America.

preventing and treating tuberculosis. Tragically, at present they are underused. For treatment to be successful six to eight months of consistent, uninterrupted medication are required. New, drug-resistant strains of the bacteria are developing because no resources are available to ensure that patients complete their treatment.

The best way to prevent the disease is to cure infectious cases at an early stage, since this also puts a stop to transmission. Control programmes should ensure that patients are cured completely and should include an education component to raise public awareness of this problem. The BCG vaccination of infants helps to avoid the most serious forms of childhood tuberculosis.

Unless we act now, we shall soon face an even greater tuberculosis crisis than that existing today. Political will is needed to reactivate the national control programmes that have become weak or have even disappeared during the past 20 years.

The World Health Organization is

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Dr Hiroshi Nakajima,
Director-General of the World Health Organization.

using its experience, contacts, organizational abilities at regional level, and political credibility in the developing world to cooperate with governments in implementing effective tuberculosis treatment and prevention programmes. Consequently, WHO is working to mobilize the resources needed to help lay the foundations for effective national control activities in the worst-affected countries.

Unless governments, public health officials and communities, including the private sector, plan an immediate and extensive response to this global emergency, tuberculosis will retain its place in history as one of the world's most devastating diseases. ■

Hiroshi Nakajima, M.D., Ph.D.

A disease that is alive and kicking

Phyllida Brown

Tuberculosis – wasn't that the disease that used to kill pale and interesting poets and novelists in nineteenth-century Europe? Yes – but if you thought TB was nothing more than a memory, wake up! The disease is alive and all too well, killing more people worldwide than any other infection including malaria and AIDS. Currently a third of the world's population harbours the tubercle bacillus and is at risk for the disease, and 30 million people will die from TB over the next decade. These numbers could continue to increase with every passing year.

In the industrialized countries, TB is back with a vengeance after 35 years of decline. In New York, one of the worst-hit areas, the number of cases of the disease has risen by 150% since 1980. But it is in developing countries that the disease continues to exact its greatest toll – more than 95% of the eight million cases and three million deaths each year. Despite the clear successes of individual nations, TB was never really eliminated anywhere, and now it is creating new crises around the world.

So what has gone wrong? The answer, say researchers, is that we made a fatal mistake: we became complacent because we thought we had beaten tuberculosis. After the discovery of effective drugs between the 1940s and 1960s, the number of cases and deaths in the industrialized countries fell rapidly. The sanatoria were closed down, public health measures for TB control were dismantled, and medical researchers working on the disease moved into other fields. Funding for TB research fell to a mere trickle as few donors

saw the need to continue. In the industrialized world, TB was presumed dead. Most health officials and scientists assumed that the developing world would subjugate the disease with equal ease using the new treatment programmes.

Both assumptions were wrong. TB treatments turned out to be less straightforward than originally supposed. TB drugs, though comparatively cheap, nevertheless represent a heavy burden on developing countries' limited supplies of foreign exchange. Moreover, the complexity and demands of organizing effective treatment services have proven difficult for many countries.

Now, doctors are relying on antiquated – but still effective – diagnostic tools, since most research on TB stopped before the era of modern biotechnology. The TB bacterium, *Mycobacterium tuberculosis*, grows extremely slowly in culture and is so infectious that only

certain laboratories are equipped to handle it. Using current methods, it can take at least two weeks to confirm TB and even longer to discover that a particular strain of the TB bacterium is resistant to a particular drug – by which time the sufferer may have already died.

Potential for rapid spread

While the world was complacent, a deadly mix of factors have combined to aid the spread of the disease. Poverty, economic recession, and malnutrition make populations more vulnerable to TB. Recent increases in human migration have rapidly mixed infected with uninfected communities. To this already explosive mixture has been added the human immunodeficiency virus (HIV), a potent and dangerous ally of the TB bacterium, so that a person infected with both the TB bacterium and HIV is much more likely to develop active tuberculosis than someone infected with the TB bacterium alone. WHO estimates that nearly five million people have already been infected with both microbes – setting the scene for a massive increase in TB cases in the coming years. In countries with a high prevalence of HIV infection, such as Malawi and Zambia, TB cases have risen sharply, sometimes more than doubling.

In addition, HIV creates particular problems for the diagnosis and treatment of TB. The skin test used to detect infection with TB is crude and basic, and often fails to work in people who are HIV-positive because it relies on measuring the response of the person's immune system. If the immune system is defective, it may not respond even though the person is infected. Furthermore, TB disease often has different clinical features in HIV-positive people. More sophisticated means of diagnosing infection in HIV-positive patients are being developed.

Treatment too is affected by HIV. For years in much of Africa, a drug called thiacetazone has been a mainstay of TB treatment. Although industrialized countries abandoned it some time ago, the drug has remained attractive to many developing countries because it is cheap. However, thiacetazone can cause severe and sometimes fatal reactions in an unacceptably high proportion of HIV-positive TB patients compared with HIV-negative patients, so doctors have warned against using it to treat TB in populations where HIV is widespread. Switching to safer drugs will cost countries money, but some doctors are adamant that a drug that is unacceptable to the West is unacceptable worldwide. And patients are less likely to come for treatment if they have valid fears about the safety of medication.

More deadly than ever

While it was always important to avoid TB infection, the incentive has now increased dramatically because of the spread of "killer" strains that are resistant to more than one of the major drugs. These multidrug-resistant (MDR) strains have probably always existed as the result of random genetic mutations, but they remained rare until the 1980s when the scene was set in the USA for them to flourish and spread.

A survey in the USA at the beginning of the 1980s found that about 7% of all TB strains tested were drug-resistant. By 1992 in New York City, more than one-third of strains tested were resistant to one drug, and almost one-fifth were resistant to the two main drugs, rifampicin and isoniazid. A few strains resist almost all the known anti-TB drugs. So far in the USA, outbreaks of MDR tuberculosis have carried an extraordinarily high death toll: more than half of those known to have been infected with MDR strains have died. Most of these deaths have been among people who were also HIV-positive, so it is difficult to estimate the overall death rate from MDR tuberculosis. However, no one knows how many people with an intact immune system have also been infected with MDR strains.

Multidrug-resistant TB has been most intensively studied in the USA and information on its spread in developing countries is still limited. However, there is evidence that MDR strains are spreading in parts of south-east Asia and southern Africa. New studies suggest that these strains are being transmitted to people who were previously uninfected.

Leading TB researchers such as Dr Lee Reichman, President of the American Lung Association, believe that MDR tuberculosis gained a foothold in the USA because of poor treatment and the collapse of the public health system. The closure of the sanatoria was supposed to have been followed by a greatly improved service in community care. But money ran out in the 1970s, and community services were actually cut. Patients who failed to complete the long and cumbersome course of treatment were often not followed up, and incomplete or inadequate treatment was just what the drug-resistant mutant bacteria needed to encourage them. Today, many health authorities employ workers to supervise patients' treatment in order to ensure that the full therapy is finished.

Still a curable disease

Tuberculosis is a terribly debilitating disease and, if untreated, kills around half of those affected. People with TB suffer from weakness and exhaustion, profuse night sweats, chest pain and cough, sometimes with bloody sputum. Occasionally the bacteria spread to affect other tissues including the bone, bringing further disability.

Fortunately, TB is still an avoidable, curable disease. With proper management, more than 95% of patients are cured. And treatment for TB costs less, in terms of the price for each year of life saved, than measles immunization. In stark contrast, the cost of ignoring TB could be catastrophic. In the USA alone, for example, which has only a tiny minority of the world's total TB cases, the direct and indirect costs of the TB epidemic since 1985 have been estimated at US\$ 640 million already, with a projected loss of \$2200 million by the end of the 1990s.

In the short term, scientists and politicians have their work cut out. More money for TB is desperately needed; better diagnostic technology and more acceptable, shorter treatment regimens will be essential. In the longer term, say health officials, countries must work to overcome the poverty that allows both TB and HIV to inflict such lasting damage on societies. ■

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What is TB and how is it spread?

Mycobacterium tuberculosis is the germ that carries TB. It is carried on droplets in the air and so can be spread by coughing or sneezing, entering the body through the airways. If the immune system fails to stop the infection, the bacteria spread around the body and destroy tissues in the lungs, where they can multiply. Large numbers of bacteria are coughed out of the lungs into the outside world, infecting others.

With appropriate antibiotic therapy, persons with TB quickly become no longer infectious. One of the most urgent research needs, say scientists and health officials, is to cut down the time needed to securely diagnose TB in almost all cases so that treatment can begin earlier. This will speed the affected person's recovery and at the same time reduce the period in which they are – often without knowing it – spreading disease.

How easy is it to catch TB? The answer depends on the two-stage process that occurs with TB; first you have to be infected, and second, the infection has to progress to disease.

Dealing first with infection, you are more likely to be infected if the person with TB with whom you are in contact (the index case) has cavities in the lungs. These will be full of bacteria and when the person coughs, the bacteria are sprayed into the air. If you inhale a bacteria-laden droplet you may become infected. Clearly, the more time you spend with this index case, and the closer contact you have with him or her, the more likely you are to become infected. Although doctors suspect that people with HIV are more likely than others to become infected, they have not yet been able to prove it.

Secondly, there is the process of the infection progressing to disease. This happens in about 10% of those infected, and it can happen at any time during the remainder of their lives. It is more likely to happen near the time the infection occurred – as time passes, it becomes less likely. However, if the immune system weakens, as happens with diabetes or cancer, or during treatment for kidney transplantation, or conditions of famine, malnutrition and, of course, AIDS, then TB can more easily develop. In people with both HIV and infection with the TB germ, as many as 8% can develop TB each year. ■



If his sputum contains bacteria, this man will spread TB by coughing and sneezing.



A laboratory technician in Pakistan examines sputum samples.

A deadly duo – TB and AIDS

Paul Nunn & Arata Kochi

The worst thing that tuberculosis (TB) control programme workers could have wished for was something that made people already infected with the bacterium many times more likely to develop active tuberculosis. That is precisely what HIV (human immunodeficiency virus) has done.

The situation is serious because about a third of the world's population, and up to 75% of adults in some developing countries, are already infected with *Mycobacterium tuberculosis*, the bacterium that causes TB. They will have got the infection from someone they know, perhaps only slightly, who has developed TB in the lungs and who – by coughing, sneezing or even just talking – spreads the TB bacteria around in tiny droplets in the air. When breathed in, these droplets enter the lungs and lodge at the deepest regions where the oxygen is absorbed. Most TB-infected people live their lives without any further problem from this infection, since the TB bacteria are caught within cells called macrophages. There they are walled off and kept quiet by the person's immunity (the T-lymphocyte, also called the T-cells) like a cobra in a basket with the lid fastened on. Consequently, in the times before HIV, only about 10% went on to develop active tuberculosis during their lifetime.

HIV is like an evil genie that goes around the body pulling the lids off all the millions of baskets. The lids are the T-cells, the crucial players in the body's immune system. HIV finds a way into these cells and forces them to produce thousands more microscopic viruses. The T-cells are then destroyed in ways that we still do not fully understand. Once the TB bacteria are set free, they can cause destruction in



When AIDS and tuberculosis strike together . . .

These two diseases amount to a double catastrophe. But tuberculosis is curable, and a good TB control programme can prevent its spread to other members of the family. This is a lesson from which decision-makers would profit.

any part of the body. Tuberculosis in HIV-infected people is often found in parts of the body other than the lungs.

A person who has been infected with both HIV and the TB bacterium may have as much as a 50% chance of developing active TB within his or her remaining lifetime, often less than 10 years. In fact, this is one of the most common diseases that HIV-infected people get. It is certainly the most

important one from the point of view of the health of the general public. This is because TB is easily passed from person to person, and it can affect HIV-negative as well as HIV-positive persons. It is not like HIV itself, where it is only through unprotected sex or transfusions of contaminated blood, or blood products, or through perinatal transmission, that you can catch the virus. After all, we all have to breathe!

Sky-rocketing figures

Without doubt, the worst-hit areas so far are in sub-Saharan Africa, and parts of the USA and the Caribbean. As many as 80% of the TB patients in some cities of Africa are infected with HIV, and nearly three times as many patients with TB are now being seen in some African countries compared with five years ago. These cases could even rise to twelve times as many!

Medical departments of African hospitals are overflowing with stick-limbed men, women and children, perhaps as many as three to a single bed, with a fourth or fifth on the floor alongside. In some big cities, nearly all of these people are infected with HIV, and perhaps as many as a half also have TB. With weakened immune systems, even those who don't have TB will soon get it in such surroundings. Often the TB goes unrecognized by doctors too busy to detect the different signs of TB in those who also have HIV. Sometimes, even when diagnosed, patients have no money for the drugs. Relatives won't help them because they have learnt from terrible experience that AIDS patients don't survive.

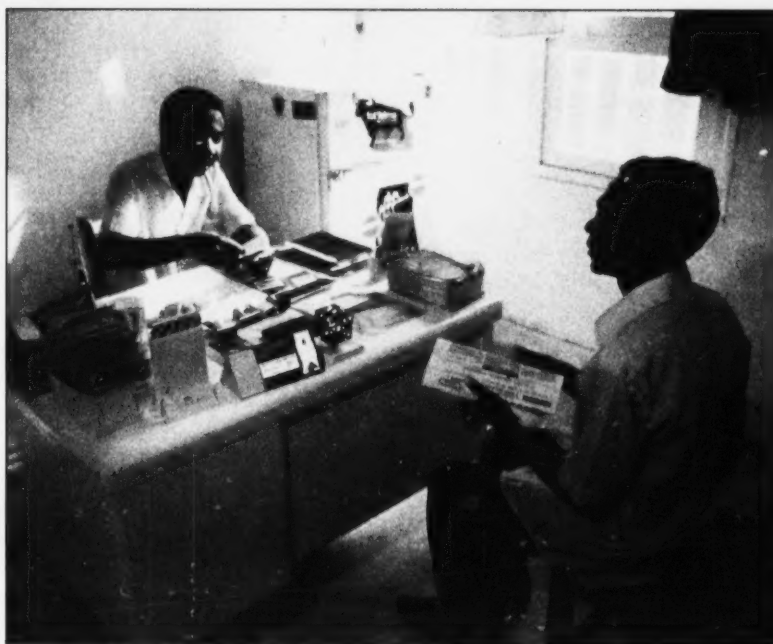
In Asia the problem has just begun. Because over half of the people in the world infected with *Mycobacterium tuberculosis* live in Asia, the potential for a catastrophe there is very high.

Treatment of patients with HIV and TB is complicated by two things – drug reactions and drug resistance. Drug reactions in TB include severe skin rashes, where the skin can actually peel right away from the body. These can even be fatal, and they happen in about 20% of people with HIV who are treated with a drug called thiacetazone, which is used in many developing countries because it is cheap and because any alternative costs at least three times more. It is hardly ever used in the richer countries.

Drug resistance has been around for many years. It happens when patients do not take their anti-TB medicines regularly right to the end of the course of treatment, either because the drugs are not available or because the patients stop taking them when they feel better – often within about a month of starting treatment. But we know from experience that you have to go right on to the end of the course of treatment to be completely cured. If you stop the drugs too soon or take them irregularly, that is when the TB bacteria can become resistant. Modern treatment using several drugs simultaneously is designed to cure the patients even if their bacteria are resistant to one drug. The new problem that was identified first in the USA is multidrug resistance where the bacteria are resistant to two or more drugs. When this occurs in someone who also has HIV infection, it is almost always fatal and it makes cure of TB extraordinarily difficult, even in non-HIV-infected persons.

TB and AIDS: a fatal combination

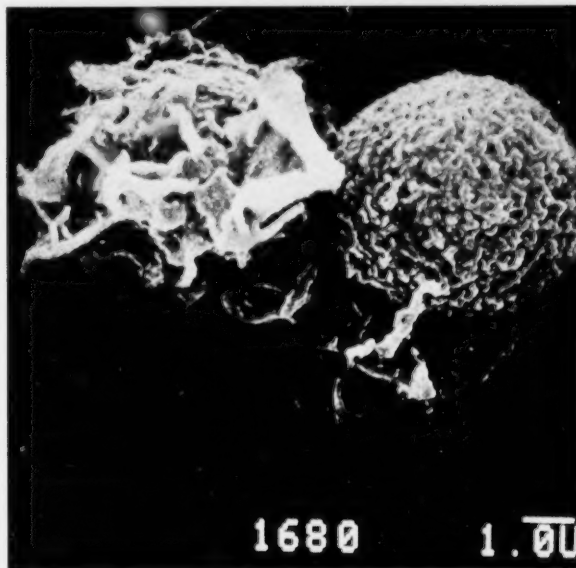
- One-third of the world's population has already been infected with TB. If these individuals contract HIV infection, it dramatically shortens their lives by causing an acute case of TB to erupt from their previously harmless infection.
- For someone who does not have a TB infection, but has contracted HIV, exposure to the TB germ can be devastating. These patients often die within weeks.
- A healthy person who has been TB-infected has less than a 10% lifetime chance of developing tuberculosis. An HIV-infected person who is also infected with TB has up to a 10% chance each year of developing a life-threatening case of TB.
- Tragic as the AIDS/TB combination is for its victims, the TB germ is an airborne risk for the community. The only protection for the community is a fast, complete cure for TB patients.



Receiving the results of a TB test. The number of TB patients in Africa has increased considerably since the upsurge of the AIDS epidemic.



TB can affect many parts of the body. Shown here is the lymph node.



A macrophage and a lymphocyte: these cells can stop TB infection from becoming disease, but are overwhelmed when HIV is also present.

What can we do?

In spite of the depressing situation that already exists in many places, there *is* an effective cure for TB. The drugs are there, they are inexpensive, the ways in which they should be used are well worked out, and methods for setting up TB control programmes have been well tried by WHO and others in many countries of Africa and Latin America. So why don't all countries have effective TB control programmes?

In the first place, the people with power to make such decisions have not realized the damage that TB can cause and is causing. Next, there are often not enough health workers with the right knowledge and experience to set up and manage such programmes. Third, there is always a lack of money to purchase the needed drugs. Politicians do not seem to realize that TB treatment is one of the cheapest and most effective ways of saving a life. And the lives are often those of young parents and workers in society. Fourth, there is a depressing pessimism about treating HIV-infected people on the grounds that they will soon die in any case. It is absolutely clear, however, that they *are* worth treating, not only to alleviate suffering associated with HIV-related diseases and to prevent

the spread of TB to others, but also because of every individual's right to cheap, effective health care.

Decision-makers should be persuaded that their people will not accept the lack of an effective TB programme.

Once the decision is made to institute a TB control programme, the guidelines recommended by WHO and the International Union against Tuberculosis and Lung Disease should be followed. These lay out very

clearly how such programmes should be set up, managed and supervised. They describe clearly how the diagnosis should be made. They tell health workers which drugs should be used and how. They make it very clear how patients should take their drugs and protect their families.

Thiacetazone should be avoided in patients who are known, or suspected, to be infected with HIV. Control programmes must plan to phase it out. For this they will need the financial support of donor countries to enable them to buy alternative drugs.

Drug resistance is best managed by prevention. This means ensuring that every patient who starts anti-TB treatment finishes it, if necessary by having health workers give each streptomycin injection and see that every appropriate tablet is actually swallowed.

Experience has shown that, at present, while AIDS is incurable, TB can be avoided in HIV-infected people. If, however, an HIV-positive person is unlucky enough to have active TB, he or she can be cured of it – and spread of TB infection to others can be prevented – by a good TB control programme. ■

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The challenge is international

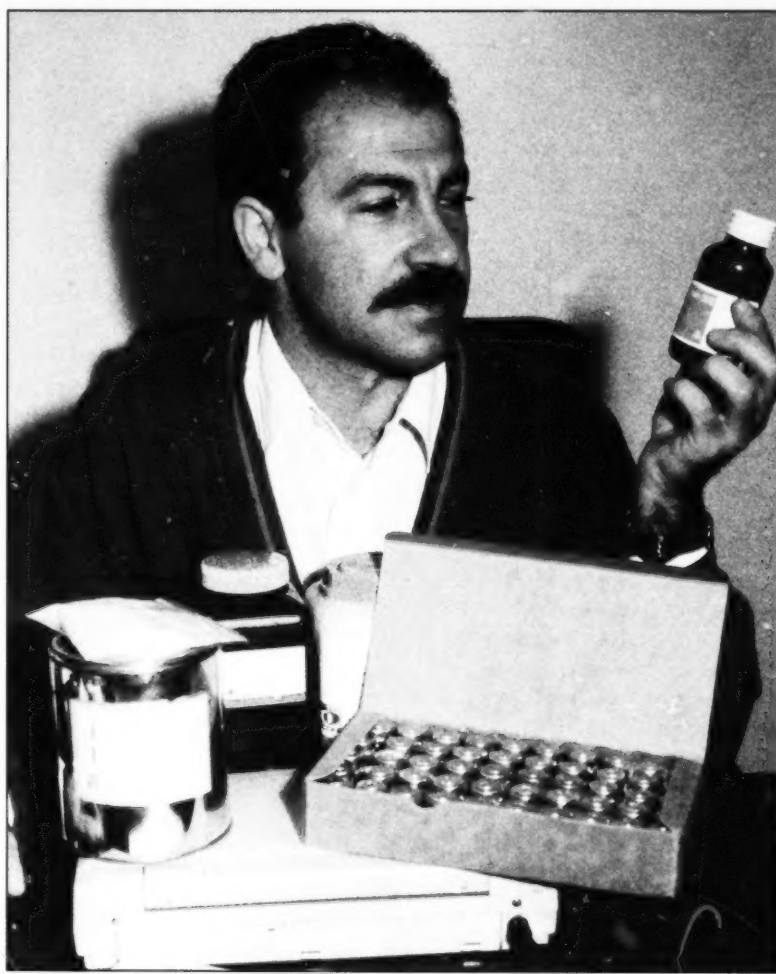
Johr Porter, Keith McAdam & Richard Feachem

Every year there are eight million new cases of tuberculosis and three million deaths. The disease accounts for 6.7% of all deaths in the developing world, 18.5% of all deaths in adults aged 15 to 59 years, and 26% of avoidable adult deaths. It is a disease which is curable and preventable, and treatment of TB is one of the most cost-effective health interventions available.

Despite these facts, tuberculosis has been comparatively neglected by the international health community over the past 20 years. An increase in the number of cases occurring in the industrialized world, the HIV-TB connection, and the spectre of multidrug resistance, has forced tuberculosis to the forefront of the international health agenda.

Now that tuberculosis is considered a health priority, what do we need to do to address this latest international public health challenge? The first step is to improve communication and encourage discussion and collaboration between the different organizations involved in tuberculosis research in order to determine how resources should be spent. These discussions need to transcend the barriers of our own particular research interests to include information and ideas from people working in other specialist fields. A multidisciplinary approach is required. It is through discussion and the exchange of ideas that progress and appropriate decisions will be made.

Among the organizations that can lighten the burden of the millions of people infected with TB are the country control programmes and the ministries of health that manage them, academic institutions, the pharmaceutical industry, international organizations, and the world political community, which must have the will to allocate the necessary resources to combat the disease.



The importance of complete, uninterrupted chemotherapy cannot be overemphasized.

"Back to the future"

To assist and encourage this dialogue among scientists in the different fields of TB, the London School of Hygiene and Tropical Medicine hosted a public health forum in April entitled "Tuberculosis - back to the future". This brought together specialists from 56 different countries, and included immunologists, epidemiologists, economists, clinicians, policy-makers, and directors of TB control programmes. The forum attempted to develop and integrate the perspectives of the different scientific disciplines in

a climate which fostered discussion and exchange of views.

There is much that we know about tuberculosis. The plenary papers described the severity of the international problem and how the interaction between TB and HIV infection has resulted in increased difficulty with diagnosis and treatment. Cost-effectiveness analysis and the use of DALYs (disability-adjusted life years) have demonstrated the economic importance of the disease and the cost-effectiveness of treatment. Adherence to drug regimens is a major problem for control programmes: new drugs which



Pakistan: examining an X-ray for signs of TB infection.



Skin tests are still widely used to detect TB infection, but do not provide definite diagnosis.

can be taken for shorter periods would undoubtedly improve adherence and reduce the problem of multidrug resistance. But many of the tools for dealing with TB have not been used appropriately and the present situation calls for new, innovative approaches.

There is also much that we do not know about this disease. We know little about immunity to TB or about the virulence of the organism. This knowledge would help us in developing improved diagnostic tools and vaccines, particularly since we have new molecular techniques to assist us.

The forum produced three messages: first, that there is an increasing international problem which has been made worse by the interaction between *Mycobacterium tuberculosis* and HIV infection as well as the emergence of multidrug resistance. Second, that research into new drugs, vaccines, diagnostics, and control programme strategy deserve a high priority. Third, that cost-effective methods for control are available but are being underapplied; we need to invest more in control methods which are already known and understood.

Four control methods

The changes in TB epidemiology described during the forum have

Did you know . . .

- TB, once thought to be under control, is fiercely on the rise in many places. Its increasing incidence affects people everywhere.
- Every year, three million people die from TB and eight million new people develop the disease. Tuberculosis is the world's foremost cause of death from a single infectious agent.
- One-third of the world's population is infected with TB.
- Tuberculosis is contagious. The disease is transmitted by bacilli spread into the air by a patient with active pulmonary tuberculosis. Coughing, sneezing, and even talking by a patient fills the air with droplets containing the TB germ.
- Once a person is infected, he or she risks developing active TB, and that risk persists throughout life.

provided the international community with a new public health challenge. At present, there are four methods for controlling the disease: improvement in social and economic conditions, case-finding and treatment, chemoprophylaxis, and vaccination.

Social and economic development is the measure that has the most profound effect in reducing the disease load; in many countries, unfortunately, such development as a means of controlling the disease must be seen as a long-term solution. In the meantime other interventions must be employed. For national control programmes, the strategies are already available. The most important is to find and treat cases of tuberculosis, and to ensure that the patients adhere to their treatment. To achieve this, innovative methods which facilitate delivery of treatment are needed – education, supervised regimens, incentives, and encouragement and empowerment will all increase patient compliance.

Priorities within tuberculosis control should continue to be case-finding and treatment with short-course chemotherapy. If resources are available, chemoprophylaxis should be given to TB-infected persons at high risk of disease and is particularly indicated for children who are close contacts of infective TB cases and persons with HIV infection. BCG vaccination is needed to protect children against the severe forms of TB such as tuberculous meningitis. National control programmes need a rational and coherent drugs policy aimed at guaranteeing the availability of essential drugs.

A wide spectrum of TB-related activities are planned or under way in many countries. New surveillance systems are being developed for drug resistance in some countries, while others are concentrating on the problems of reactivation in persons with HIV infection by studying preventive treatment. In the field of compliance, some tuberculosis programmes are looking at education to improve compliance, others at supervised regimens and incentives, and still others at encouragement and empowerment. The education is being targeted at influential groups such as politicians, community leaders and groups at high risk of the disease.

For the laboratory research scientist, there is the challenge of using modern biotechnology to regenerate the scientific impetus and breadth of vision characteristic of TB research in the earlier part of this century, and of applying these advances to developing countries. If this can be done there is the chance of a new vaccine, of new methods for determining protective immunity and of using this information to reinforce the body's natural ability to cope with infection. Research can help us to understand the virulence of the tubercle bacillus, and to develop new diagnostic tools and rapid tests for drug resistance.

TB can be cured inexpensively

- TB has a cure, and treatment is inexpensive.
- TB control is a very cost-effective health intervention. Its cost-effectiveness is equivalent to that of the well-known childhood immunization programmes.
- Successful treatment requires 6-8 months of consistent, uninterrupted medication.
- Successful treatment demands education and follow-up.
- New, drug-resistant strains of TB are developing because patients are not completing their treatment. These drug-resistant strains are significantly more dangerous to the individual and the community because they are more difficult and more expensive to treat.
- The best way to prevent TB is to cure infectious cases in their early stages in order to prevent transmission to others.
- TB control programmes that treat infectious patients but don't ensure that they are cured risk doing more harm than good. Patients who have incomplete treatment can develop - and spread - drug-resistant TB.
- The World Health Organization's TB Programme is working with governments to develop effective control activities. With rigorous monitoring and evaluation procedures, these programmes will have a tremendous impact on the disease.

Industrial partners

The pharmaceutical and vaccine industry also has an important role. It needs to forge new partnerships with academic and international organizations, and to increase communication with countries where TB is common. Research needs to be

directed at providing appropriate, inexpensive medications for control programmes worldwide. New drugs need to be developed which can destroy latent infection, and which require only days or weeks of therapy rather than months. Research will inevitably be conducted in areas of the world where TB is common. Funds need to be targeted at drugs which will provide treatment for the many rather than for the selected few in the industrialized world. International purchasing consortia may be required to give confidence to the private sector concerning the market for new drugs and vaccines, and thereby to stimulate the necessary investment in research and development.

The public health community has already managed to direct the attention of politicians to the increasing problem of TB, but there continues to be a need for better dialogue between the health community and the political community. Politicians need to be reminded of the association between the disease and poverty, and of the continued need to target energy and funds at the poorer areas of the world where TB is found.

The energy and enthusiasm are there among the multidisciplinary groups of health care workers and scientists working on tuberculosis. Politicians can harness this energy and enthusiasm by providing resources to support control programmes as well as funds to answer both operational and basic scientific research questions. Most essential are communication and cooperation between public health practitioners, scientists, the pharmaceutical industry and politicians, aimed at developing a cohesive strategy to deal with this international public health challenge. ■

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WHO's role in tuberculosis research

Richard J. O'Brien

Although significant advances in the fight against tuberculosis (TB) may be made by proper application of existing diagnostic and treatment technologies, considerably more progress might be possible if new tools were available. The most commonly used diagnostic tests – sputum smear microscopy, culture of mycobacteria for identification and tests for TB drug sensitivity, tuberculin skin testing, and chest radiography – are decades old and suffer from various drawbacks.

Smear microscopy, while identifying the most infectious cases of pulmonary tuberculosis, is not sensitive to low levels of disease and requires well-maintained equipment and well-trained laboratory workers. Culturing and drug susceptibility testing call for even more expertise, require up to two months to give

results, and cost still more. Tuberculin skin testing is primarily used in surveys to estimate the risk of infection, but it is not sufficiently accurate to be useful as a diagnostic test for active disease. Chest radiography is expensive and generally available only in hospitals and specialized diagnostic centres. Furthermore, there is evidence that over-reliance on radiography leads to over-diagnosis of tuberculosis and unnecessary expenditure on drugs and on staff time. It may also not be able to detect the early stages of disease. Thus, new, simple and rapid tests would significantly improve tuberculosis diagnosis.

Modern short-course therapy for tuberculosis works very well but requires patients to take medication regularly for at least six months to be cured. Not surprisingly, patients all

too often stop taking their medicine prematurely. Furthermore, in some countries drug-resistant TB appears to be on the increase. Tuberculosis drugs may also be used to treat persons infected by the tubercle bacilli before they develop the active disease. This preventive chemotherapy may be useful in limiting the increase in tuberculosis due to HIV infection, but again it involves taking medication for relatively long periods and its cost-effectiveness remains to be determined. It is clear that new drugs are needed to shorten current therapy, to improve preventive therapy, and to treat persons with drug-resistant TB.

Finally, although BCG vaccination has been widely applied, it has had little apparent epidemiological impact on tuberculosis incidence. Because BCG does prevent serious and often fatal forms of tuberculosis in young children, its use in newborn children is still vital. However, research is badly needed to develop new, effective vaccines against tuberculosis. Especially beneficial would be a vaccine which is capable of protecting already infected persons from developing the active disease.

WHO's involvement

For these reasons, WHO's Tuberculosis Programme is actively promoting the development and assessment of new tools for the diagnosis, treatment and prevention of tuberculosis. Clearly, tuberculosis research will be most economically and easily conducted in countries where the disease is most prevalent. This is especially true for clinical therapy trials, which involve comparison of a new drug or a new drug regimen with standard treatment, and require substantial numbers of patients to be followed for relatively long periods of time. Although there

are existing infrastructures to support these types of trials in developed countries, it would be difficult for investigators in those countries to recruit the required number of patients and follow them for the required period.

Given the scarcity of resources available for TB research, it is imperative that the global research effort be properly coordinated, avoiding unnecessary duplication and helping to ensure that funding is being applied to the studies of greatest importance. WHO's Tuberculosis Programme has taken on this coordinating role, with an emphasis on studies which may yield results in three to five years and which are of special relevance to developing countries hardest hit by tuberculosis. Chosen as the most important research areas are:

- laboratory and clinical studies of both existing and promising new anti-TB drugs and drug regimens, new methods of drug delivery and new ways of stimulating the body's immune system to improve treatment;
- the development and assessment of new, rapid diagnostic tests for active tuberculosis and TB infection;
- epidemiological studies using new techniques (such as DNA "fingerprinting") to improve TB control, and studies to define better the groups and individuals at increased risk of tuberculosis;
- studies on the interaction of tuberculosis and HIV infections that would have direct and immediate application to national tuberculosis programmes.

Funding prospects

In the past it proved difficult to attract funding for research studies. Fortunately, with the successful initiation of the research programme, the prospects for increased funding are good. The most critical need for research and development studies is the availability of a laboratory capable of isolating and identifying *Mycobacterium tuberculosis*, and of reliably performing drug susceptibility studies. Development of research and

laboratory infrastructure will be an important component of future activities.

The research component of WHO's Tuberculosis Programme works closely with WHO's Global Programme on AIDS in the management of the TB-related portion of HIV research. Support has been provided to monitor HIV-associated tuberculosis trends in Uganda and the United Republic of Tanzania, and to determine the infectiousness of HIV-associated tuberculosis in the Dominican Republic. The research in Africa has demonstrated the tremendous impact of HIV on the tuberculosis problem. Studies to evaluate the efficacy and toxicity of short-course chemotherapy in HIV-infected TB patients are under way in Haiti (in adults) and the Dominican Republic (in children). Another paediatric study in Zambia has shown that fatal skin reactions occur frequently in children treated with the anti-tuberculosis agent thiacectazone, and has led to a change in WHO recommendations on TB therapy for persons who are also at risk of HIV infection. A unique study in Uganda to evaluate the operational feasibility of isoniazid preventive chemotherapy for HIV-infected persons is critical to the process of assessing new public health policies which could emphasize

the role of TB prevention for high-risk populations in the developing world.

In the area of diagnostic studies, close cooperation is maintained with the tuberculosis component of the WHO/UNDP Programme for Vaccine Development, and support has been provided for assessment of new tests such as PCR (polymerase chain reaction) for TB diagnosis. In the field of drug development, WHO-supported studies have shown the potential of the new quinoline derivative, sparfloxacin, for tuberculosis treatment, and the great activity of a new rifamycin antibiotic, rifapentine, for tuberculosis preventive therapy. A comprehensive, global drug development plan has been proposed, specifying the role of WHO in this activity, and emphasizing the coordination of clinical therapy trials through a network of collaborating centres.

Clearly there are tremendous challenges to be met in tuberculosis research, and WHO believes that, with the help of the global research community, it will make an important contribution to the advance against this old disease. ■

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There is a need to identify better the groups of people most at risk of tuberculosis.

BCG – a partial solution

Gerard Ten Dam

BCG vaccination has been used extensively to prevent tuberculosis, first in mass vaccination campaigns and more recently in vaccinating newborn babies. However, its role in control activities is often not understood.

A first infection with the tubercle bacillus produces a certain level of cellular immunity but also carries the risk of causing active disease. BCG vaccination is given to produce the immunity without the risk of disease. BCG therefore can only protect those who are still uninfected; it cannot protect people who are already infected or those who could develop TB as a result of reinfection. Consequently, the contribution that BCG can make to TB control is limited, since most cases occur among those already infected (one-third of the world population is already infected) and reinfection among adults may be quite common. Moreover, many people, especially in tropical countries, have a certain degree of natural immunity against tuberculosis derived from infection with environmental saprophytic mycobacteria. These variables in the TB ecosystem, as well as possible differences in the efficacy of BCG vaccines, explain the apparently controversial results observed in community trials of BCG vaccines.

Since BCG should be given before infection, it is indicated *a priori* for young children. Recent case/control and contact studies have shown that it provides substantial protection, especially against the serious disseminated forms such as tuberculous meningitis and miliary disease, which are most frequent among young children and are often



Children waiting in line for BCG vaccination in Chile.

fatal or leave sequelae, even if treated with modern drugs.

BCG vaccination should therefore be given as early in life as possible in any situation where the risk of TB infection is high or is rapidly declining but still exists. Prevention of childhood TB does not diminish the transmission of infection in the community because the most common forms of childhood TB are not infectious. However this does not imply that vaccination during childhood has no further contribution to make to TB control. BCG prevents blood-borne spread of an infection, and thus not only the immediate serious forms of childhood TB but also the establishment of foci, mainly pulmonary, which may produce disease later in life. This is called endogenous reactivation. It is interesting to note that when the risk of infection has become very low, practically all TB cases occur as a result of endogenous reactivation. So case-finding and treatment (generally considered the major TB control measures) will have less impact on the incidence, and preventive treatment will be less feasible because

of the low risk among the still large numbers of infected individuals. However, BCG vaccination given early in life – with its lasting effect on endogenous reactivation – will continue to reduce the incidence and thus hasten the eventual elimination of the disease.

Uninfected individuals in contact with TB patients are at a high risk of contracting the disease. Among them, notably medical personnel, screening for infection and preventive treatment is now often applied in preference to BCG vaccination, the efficiency of which has proved to be doubtful in adults. The emergence of infection with multidrug-resistant bacilli, however, has brought this practice into question.

BCG vaccination may cause disseminated BCGitis – illness caused by the vaccine itself – in cases of severe immunodeficiency. This has become of concern in view of the HIV-infection and AIDS epidemic. Several cases have been reported in HIV-infected infants but it was not observed in prospective studies. BCG vaccination continues to be recommended for asymptomatic children in countries where there is a high risk of TB infection. Where the risk is low, BCG may be withheld from children known or suspected of being HIV-infected. BCG should never be given to symptomatic HIV-infected individuals.

The best way to go about controlling tuberculosis is targeting infectious people in the community and providing them with treatment. ■

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Challenge in Tanzania

Petra Graf & H. T. Chum

The United Republic of Tanzania in 1977 established a National Tuberculosis and Leprosy Programme (NTLP), which is probably the first combined leprosy/TB programme of its kind in the world. The programme has operated successfully during the last 16 years in controlling these two chronic infectious diseases which are of major public health importance. What is the secret of its success?

Despite its poor resources Tanzania has had political stability over many years, and also has a well-established health infrastructure from central to district levels and down to local dispensaries. The NTLP is fully integrated in this existing health system; no extra structures had to be created.

From the beginning, the

While tuberculosis is sure to continue in Tanzania because of the unfortunate link with the HIV epidemic, officials with the national control programme are convinced that the disease can be controlled – given continuing support from the government and the donors.

programme has had the full commitment and support of the government. Almost all staff are Tanzanian, their salaries being paid by the government. A continuous,

uninterrupted drug supply from overseas donors has guaranteed that patients looking for treatment do really get it. In addition, reliable transport (cars and motorbikes), which is one of the biggest cost factors besides drugs, has been made available by the donors. Regular training, refresher courses and systematic supervision from the beginning has helped to motivate all levels of staff, and to make the programme a success.

As such, it has served as a model for many other countries. The uniform recording and reporting system designed by the International Union against Tuberculosis and Lung Diseases (IUATLD), under the guidance of Dr K. Styblo, is used nowadays – with only slight variations – in many national TB programmes

and represents WHO's recommended recording and reporting system. Moreover, the NTPL has been the platform for the IUATLD's international course on tuberculosis since 1990.

Why are cases increasing?

The two pillars of the NTLP are case-finding and treatment. Ideally and in theory a programme should:

- find all TB cases;
- treat all of them until cured and thus eliminate a source of infection to others;
- monitor the results achieved in each district to maintain high rates of cure.

Infectious cases are considered to be those patients with TB of the lung, who cough up many tubercle bacilli which can be seen if the sputum is examined by microscopy. These patients are termed smear-positive pulmonary TB cases.

Our estimate for Tanzania is that:

- 80% of all TB patients have been found;
- 90% of them have been treated;
- 80% of the infectious cases have been cured.

These results should normally lead, after some years of proper management, to a steady drop in the

risk of infection and to fewer new TB cases. Instead we find a rapidly increasing number of new TB cases. Reported TB cases in 1991 numbered 25 210; in 1992 they were estimated at 27 000, and in 1995 there will be an estimated 36 000. Why is this so?

Preliminary results of a still continuing WHO study in Tanzania reveal a close association of HIV infection and TB. About 30-40% of our TB patients are HIV-positive. When their immune system becomes depressed, they are much more likely to develop active tuberculosis.

Heavier case-load

Although the response to chemotherapy in TB patients who are HIV-positive is generally good, the TB part of our programme is confronted with an increasing case-load year by year. The number of TB cases found in Tanzania more than doubled between 1983 – when the first AIDS case was detected – and 1991, when a total of 25 210 TB cases were notified.

In the first years of the programme (1977-83) it was the quality of the service offered that attracted more and more patients and led to increased case-finding. This is still true to some degree, but at present up to 30% of the

TB cases notified in Tanzania are related to endemic HIV infection. The latter is the most important risk factor so far identified to turn latent TB infection into active tuberculosis. Some 40-50% of all Tanzanians aged around 40 years are infected with the tubercle bacillus, but only a few actually develop the disease. When such TB-infected – not TB-diseased – people acquire HIV infection, the tuberculosis quickly emerges and they become very ill.

Tuberculosis is one of the early opportunistic infections in HIV patients, a so-called "marker" disease. It is the only opportunistic infection in HIV patients which can be transmitted to a healthy population. It is therefore in everyone's interest to control TB.

What can we do to overcome the problem of rising figures for TB? The most important step is to cure as many smear-positive patients (the source of infection) as possible by early, adequate and regular treatment. This also prevents development of resistant TB germs to the few drugs available for treatment of TB.

For many years in Tanzania, around 80% of all patients who had short-course chemotherapy were able to be cured. Last year, of the 8% of patients who died during treatment, many died from causes other than TB; a good number of them died from



Collecting sputum samples



Examining patients' sputum for TB bacteria – the sure way to detect an infectious case.

AIDS after being successfully treated for TB. However, a good TB programme would be unable to influence this proportion.

Cost-effective strategy

Good programme results (80% of infectious patients cured) can only be maintained by adjusting the numbers of staff with the increase of TB patients, making enough space available for patients in treatment facilities, guaranteeing funds for drugs for all patients (drug costs alone for one patient on short-course chemotherapy are about US\$ 30), and finding new ways of managing the numerous cases (such as decentralization of treatment facilities or integration with private institutions); health education is also important.

TB is still the second most important killer in Dar es Salaam, the largest city, which in 1992 harboured 6000 TB cases out of a total of 27 000 for the whole country. It ranks among the top five diseases in the 20 regions of Tanzania and therefore has a very high priority in the country's health services as well as in primary health care activities. The average costs per patient cured, including drugs, staff salaries, transport, and use of hospitals and other treatment facilities, are around US\$ 200. Treatment of TB is a very cost-effective health intervention.

Although TB occurs in children, it is very rarely infectious and can easily be cured if treatment is given. The largest proportion of lives saved are among the adult population, since TB affects mostly adults in Tanzania as it does elsewhere in the world. Early diagnosis and effective treatment will not only enable men and women to do their jobs again, and mothers to bring up their children – often in extended families – but also contribute to a more stable social structure even in the face of the AIDS epidemic.

There is no doubt that endemic TB will continue in Tanzania, because of the unfortunate link with the HIV epidemic. This is a real challenge to all aspects of the programme, and will call for a large input in operational research in order to find strategies to cope with the new situation. Still, TB can be controlled even now:

- if we continue to keep – maybe in a modified manner – the already established services for diagnosis and treatment with a high level of quality;
- if people still trust the programme and come forward for treatment;

- if the commitment of the Tanzanian government and of the overseas donors (International Union against Tuberculosis and Lung Diseases, the Swiss government, the German Leprosy Relief Association, the Netherlands TB and Leprosy Relief Associations, and WHO) continues to be firm. ■

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A woman receives streptomycin as part of her treatment.

Multidrug-resistant tuberculosis

Sriram Prasad Tripathy

Multidrug-resistant TB has recently been recognized as a major problem in the USA. It has reached crisis proportions in New York City and in a few other cities, particularly among persons with HIV infection. There, an inadequate public health infrastructure and earlier lack of resources have impeded efforts to control the spread of these strains, which have been implicated in TB outbreaks in prisons, nursing homes and several hospitals.

Since these strains are resistant to isoniazid and rifampicin, the two most powerful and most commonly used antituberculosis drugs, the disease is particularly difficult to treat and prevent, even in the absence of HIV infection. Associated mortality among persons with HIV infection has been in excess of 70%, and deaths have been reported among medical personnel and others working with TB patients. Although this problem has been most extensively documented in New York City, it can certainly occur in other countries and other settings, as recent reports from France and Italy demonstrate.

How does multidrug resistance develop? An average of 100 million TB bacilli are present in the lungs of a person with new, untreated tuberculosis. Because of individual mutation, a small number of these bacilli may be naturally resistant to one of the main antibiotics such as isoniazid, rifampicin, pyrazinamide or ethambutol. When these powerful drugs are used together, they will essentially kill all the TB bacilli, as the risk of natural resistance to more than one drug occurring at the same time is very low. However, if a patient takes a single drug or takes the required drugs for less than six months, which is the



Drugs must be taken regularly for at least six months to achieve a complete cure.

minimum recommended duration of treatment, some bacilli may survive and multiply undisturbed in large numbers. Resistance to isoniazid, for example, is commonly created in poorly managed TB programmes.

Poor chance of survival

When bacilli resistant to isoniazid multiply to sufficient numbers, the patient starts feeling sick again. If treatment of this second episode of illness is not completed or is inadequate, some surviving bacilli may become resistant to a second drug as well. If a third episode of illness is also treated inadequately, eventually a high proportion of the remaining bacilli may become resistant to more than two drugs. At this point, the patient has a full-blown case of multidrug-resistant TB, and cannot effectively be cured by the four main antituberculosis drugs; the survival prospects are very poor.

Other drugs can be used, but the chances of curing the disease are much decreased, since the most powerful agents no longer work against these bacilli. In addition, resistance to the new drugs employed is likely to emerge. Finally, the risk exists that the patient with multidrug-resistant TB will pass the infection to others in close contact. In that case, the newly infected person will be multidrug-resistant from the outset.

The lesson being learned in the USA should be heeded in all countries where TB is a public health threat. Although most developing countries do not yet have a severe problem of multidrug-resistant tuberculosis, the increasing use of rifampicin in tuberculosis control programmes may see the widespread emergence of resistant strains in the future if these programmes are not very well managed. As for the other industrialized countries, it is obvious that any effort to decrease attention to tuberculosis control in areas where tuberculosis incidence is at present low can meet with disastrous consequences. ■

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TB revisits the industrialized world

Hans Rieder & Mario Raviglione

The decline in tuberculosis incidence observed for several years in industrialized countries appears to have slowed or even reversed.

A great deal of attention has been given to the increase of tuberculosis in the USA, which was first noticed in 1986. Similar increases are occurring in other industrialized countries, including some in western Europe. This article will summarize the extent to which the TB epidemic has returned as a public health threat to industrialized countries.

USA. Between the 1950s and 1985, TB notifications decreased at a steady rate of 5% each year. However, between 1985 and 1991, TB notifications increased by 18%, resulting in an additional 39 000 unexpected cases of TB. Over half of these new cases were found among 25-44-year-olds. Of the 26 283 new TB cases in 1991, two-thirds occurred among racial and ethnic minorities, and over a quarter among immigrants.

It is believed that infection with the human immunodeficiency virus (HIV) has largely contributed to the increasing trend: 4.3% of all AIDS patients suffer from TB. Likewise, 11% of all TB cases are HIV-positive; in certain areas of the country the rate is as high as 50%. Homelessness, drug abuse, deterioration of living conditions and of health care delivery to people, and immigration have also been implicated as factors contributing to the rapid increase of TB in the USA.

Western Europe. In recent years, increases in tuberculosis case notifications have been recorded in Denmark, Ireland, Italy, Netherlands, Norway, Spain and Switzerland. TB case notifications have levelled off in Austria, Sweden and the United Kingdom, and continued to decline in Belgium, Finland, France, Germany,

and Portugal. The highest case rate was found in Portugal (57.6 per 100 000 population in 1991) and the lowest in Denmark (6.5 per 100 000 in 1991). However, all countries except Portugal reported rates lower than 25 per 100 000.

Deaths due to tuberculosis have uniformly decreased in all countries. The highest death rate was in Portugal (2.8 per 100 000 population in 1990) and the lowest in the Netherlands (0.3 per 100 000 in 1989). All other countries had death rates below 2.4 per 100 000.

Among the indigenous population of most western European countries, tuberculosis has become a disease of the elderly. The notable exception is Portugal where in 1990 over half the cases occurred among 15-44-year-olds. In Denmark, Netherlands, Norway, Sweden and Switzerland an increasing number of cases among foreign-born people has changed the expected downward trend. HIV infection appears to contribute only marginally to overall tuberculosis morbidity, but it is important in parts of France, especially Paris and surrounding areas. Tuberculosis is also common among HIV-infected persons in Italy, Portugal and Spain.

Australia. Case notifications have slightly increased from 5.6 (per 100 000) in 1986 to 5.9 in 1990. Increases in new case rates have been seen in New South Wales and Queensland. In 1991, 15-44-year-

olds accounted for 41% of all cases, and those aged over 64 years for 26%. Foreigners (mainly from south-east Asia) constituted 66% of all cases in 1991, and Aborigines only 15% of the cases among Australians. Death rates have remained constant between 0.3 and 0.5 (per 100 000) during the past ten years. The impact of HIV on the TB situation in Australia is limited: only 2.5% of TB cases in New South Wales were HIV-seropositive in 1991, and only 0.4% of all AIDS cases so far reported had TB.

New Zealand. There were 335 TB cases in 1991 at a rate of 9.9 per 100 000. TB mortality rates decreased from 0.9 to 0.5 (per 100 000) during the period 1980-88; in 1991, the rate was 0.4.

Canada. The number of TB case notifications and rates has stagnated over the past six years. In 1991 there were 2044 cases reported (rate 7.6 per 100 000). TB mortality rates have been constant between 0.4 and 0.6 (per 100 000) since 1980. By population groups, cases have remained fairly constant among native Canadians (i.e., Indians and Eskimos) and the foreign-born, while they have regularly decreased among non-native Canadians. The foreign-born constituted 48% of all cases in 1989, and natives 20%.

Japan. Japan is epidemiologically similar to those European countries,

like Germany, that are still experiencing a regular decline of tuberculosis cases. In 1991 there were 50 612 cases (rate 40.8 per 100 000). The downward trend of TB notifications continues in Japan, with an average decline of 3.5% per year between 1980 and 1991. This decline, however, is smaller than that during 1962-80. Smear-positive cases have regularly increased since 1980. In general, mortality rates have been decreasing at about 4.6% per year since 1980. The TB mortality rate has decreased from 3.0 per 100 000 in 1990 compared to 2.7 in 1991. There has been no increase by age groups, although the rate of decline is slowing down in adults. No impact of the HIV epidemic on TB has been noted.

Conclusion

While TB continues to decrease in Belgium, Finland, France, Germany, Japan and Portugal, increases have been seen in the Scandinavian countries, Netherlands, Switzerland and the USA. A levelling-off is evident in all the other industrialized countries. The increase in TB in many industrialized countries is mainly due to two factors: rise in TB incidence among the foreign-born and the HIV epidemic. However, the latter seems to have had an impact only in the

USA and in certain cities of western Europe.

It is still possible to reduce TB in industrialized countries, provided that immediate steps are taken on a number of fronts. First, attempts should be made to control the disease among immigrants. Second, measures should be implemented to reduce the TB incidence among HIV-infected people. Third, the TB surveillance systems of different nations must be coordinated. And finally, industrialized nations must address the much more severe TB epidemic faced by developing countries, as the global spread of this highly contagious disease directly relates to their own TB situation. The longer industrialized nations wait to fight the TB crisis, the more costly the epidemic will be later, in terms of both public health budgets and human lives. ■

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Brief history of an age-old disease

The captain of all these men of death that came against him to take him away was the consumption; for it was that that brought him down to the grave.

John Bunyan,
The life and death of Mr Badman,
1680

The origins: Humanity has probably recognized tuberculosis (TB) as a killer disease since the last Ice Age, if not before. Traces of tuberculosis lesions have been found in the lungs of 3000-year-old Egyptian mummies. The Greek physician Hippocrates (460–370 BC) – “the father of medicine” – wrote a description of the disease.

Name: In Classic Greek times it was known as *phthisis*, from the verb *phthinein*, to waste away. Right up to the present century, it was commonly called consumption – for the same reason. But it was in the 17th century that a Dutchman, Franciscus Sylvius of Leyden, first used the term “tubercle” to describe the knobby lesions found in the lungs of people who had died of the wasting disease. The name tuberculosis seems first to have been used in 1839, by Johann Schönlein.

The bacillus: In 1882, German physician Robert Koch announced the discovery of the tubercle bacillus, and published an article entitled “Etiology of tuberculosis”. Within eight years he was able to make an extract of dead bacilli to form tuberculin, which could then be used as a diagnostic test for tuberculous infection. Koch was awarded the Nobel Prize for Medicine in 1905. Today the bacillus responsible for TB is called *Mycobacterium tuberculosis*.



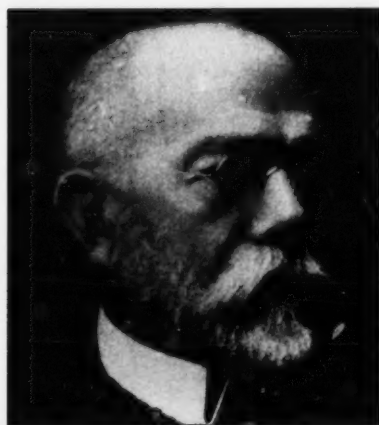
In the 1950s, tuberculosis patients were confined to bed and told to breathe the fresh air in sanatoria built in the mountains.

X-rays: Wilhelm Conrad Roentgen discovered the use of X-rays in 1895 and made it possible for the first time to visualize the chest of living persons for signs of tubercular lesions. His Nobel Prize for Physics was awarded in 1901.

A vaccine: In 1921, French scientists Albert Calmette and Camille Guérin created a vaccine against tuberculosis from an attenuated form of the bovine bacillus. BCG, standing for *Bacillus-Calmette-Guérin*, is still the only vaccine we have against the disease.

A first drug: Selman A. Waksman and his colleagues, working in the USA in 1944, discovered streptomycin, the first antibiotic effective against tuberculosis. Waksman received the 1952 Nobel Prize for Medicine.

Mass vaccination: The first mass vaccination campaign was carried out in 1948–51 by the Scandinavian Red Cross Societies, with the support of UNICEF. From 1951 it became the responsibility of WHO, which helped governments progressively to



Robert Koch (1843–1910), discoverer of several bacilli, among which was *Mycobacterium tuberculosis*, which he identified in 1882.

undertake their own BCG programmes.

Sanatoria: For more than a century, physicians used to send TB patients for rest and exercise to sanatoria, often in mountain areas where there would be plenty of fresh air. By 1960, it became apparent that these cases could be treated with the new anti-TB drugs just as effectively in their own homes. Sanatoria began to close all around the world.

HIV: While TB remained a major health problem in the developing countries, from the mid-1980s the advent and spread of HIV, the virus that leads to AIDS, paved the way for TB to stage a comeback in the industrialized countries, and thus on the world scene.

Chemotherapy: Today, WHO recommends short-course chemotherapy as the most effective way of curing every infectious patient and preventing the spread of tuberculosis in the community. Cure is easily achieved through the use of modern medicines – treatment with four or five widely available inexpensive drugs, which can cure over 90% of TB patients in the developing world – provided they are continued for a minimum of 6 months. (See page 25)

Death of poets:

[In the early 1820s] it was all the fashion to suffer from chest complaints; everyone was consumptive, poets especially; it was good form to die before reaching the age of thirty.

Alexandre Dumas père,
Mémoires, 1854

And TB did indeed kill – at all too young an age – poets, artists, musicians. Among the many whose lives were cut short were painters Antoine Watteau and Amedeo Modigliani, poet John Keats, composers Carl Maria von Weber and Frédéric Chopin, South American liberator Simon Bolivar, writer Anton Chekhov and philosopher Henry David Thoreau. Tens of millions more fell victim to TB before they had a chance just to live a normal life span.

If we are continually guided in this enterprise by the spirit of genuine preventive medical science; if we utilize the experience gained in conflict with other pestilences, and aim – with clear recognition of the purpose and resolute avoidance of wrong roads – at striking the evil at its roots, then the battle against tuberculosis cannot fail to have a victorious issue.

Robert Koch,
The fight against tuberculosis, 1902



The bacilli of tuberculosis as Koch saw them under the microscope.



Mycobacterium tuberculosis, enlarged 12 000 times by an electron microscope.

A success in China

Yin Dakui

High levels of tuberculosis are prevalent among the rural population of China, with deaths averaging about 250 000 a year for the last decade. In the past, the country's tuberculosis programme was inadequately funded, but a substantial loan has now been obtained from the World Bank to revitalize the programme in 12 provinces with a total population of 550 million. This seven-year project will cost an estimated US\$ 113 million, 50% being covered by the World Bank loan and the rest provided by provincial and local governments.

The objective is to reduce sharply TB as a leading public health problem by effectively curing infectious patients, thereby stopping transmission of the disease in the community. This will involve improving case detection in the participating provinces and increasing the cure rate of newly diagnosed

smear-positive pulmonary TB cases from less than 50% before the project to over 90%. The main strategies are passive case-finding, diagnosis by sputum smear, and fully supervised short-course chemotherapy directly administered to the patient by village doctors. The drugs are provided in blister packs to simplify and ensure their delivery and administration to the patient directly by the village health worker. Small financial incentives will encourage peripheral health staff to detect and cure infectious tuberculosis patients.

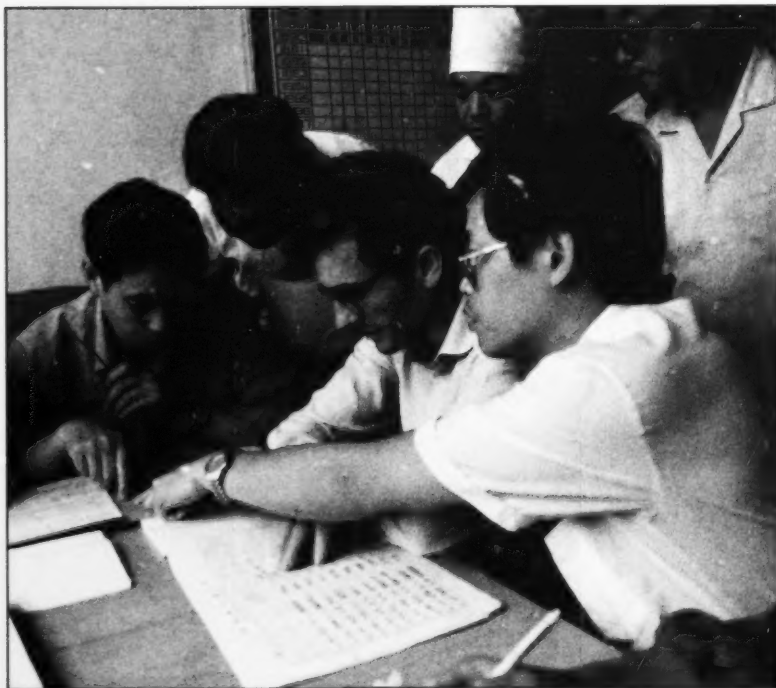
The programme started during the second quarter of 1991 in five pilot counties of Hebei Province. Preliminary results showed that the technical strategy would work. In 1992, the project started in all 12 participating provinces, with WHO's Tuberculosis Programme providing technical assistance to the World Bank in assessing progress and trouble-shooting.

Some 20 000 new and previously treated cases were diagnosed in 1992. In addition, a large number of cases already known but lost to follow-up in the earlier programme proved to be still infectious and therefore received a strong retreatment regimen.

Positive results

The project has already successfully helped more than 90% of newly diagnosed cases and 72% of the retreated cases (patients who failed with chemotherapy before the project and those who relapsed) to become non-infectious and well on the way to cure. By the time treatment is completed the results among these patients are expected to be similar to those in the pilot areas, where cure was achieved in 96% of new patients and in 81% of retreated cases.

Most of the 96 counties which embarked on the project in 1992 completed training and started case-finding and treatment activities during the second quarter of the year. Case-finding reached its peak in the third quarter, and so did the detection of new smear-positive patients. The larger proportion (41%) of newly detected smear-positive cases fell within the age group 25-44 years. Overall there were 27% more men than women; whether this phenomenon is due to lower detection or a true lower incidence of tuberculosis in women remains to be investigated. But in both developed and developing countries a lower incidence among women aged 30 years and over has been observed.



A countrywide TB programme needs regular planning meetings.

Intensive advertisement of the new programme particularly attracted those patients who had failed to be cured before the project began. These cases are the most difficult to cure because they harbour bacilli that are usually resistant to one or more drugs. Such a large number of failure cases in the initial period of the project may not necessarily be favourable to its reputation because a proportion of patients will not improve, as compared to newly diagnosed patients who have high chances of cure. It is interesting, though, to observe that the reservoir of such "difficult" patients seems to be going down quickly.

Among a cohort of patients registered from April to December 1991 in the five pilot counties of Hebei Province and evaluated 12–15 months after registration, the cure rate was 96% for new patients (removing from the denominator nine cases who died during chemotherapy), 83% for relapsed patients, and 81% for other retreated cases (again excluding patients who died). It is significant that in the pilot areas no patient was lost to follow-up.

A pattern for Asia

China established this project with the aim of organizing effective cure of TB patients, thus preventing transmission of the disease. The project's success is proving that we can control TB now, particularly in the most deprived rural counties which earlier had poor control programmes.

The assistance received from the World Bank and WHO has created the necessary momentum for reorganizing the structure of tuberculosis control in the participating provinces and at the same time for effectively introducing new WHO policies. The organization of case-detection and supervision of patients at village level responds to their needs, and is fully in line with the primary health care approach.

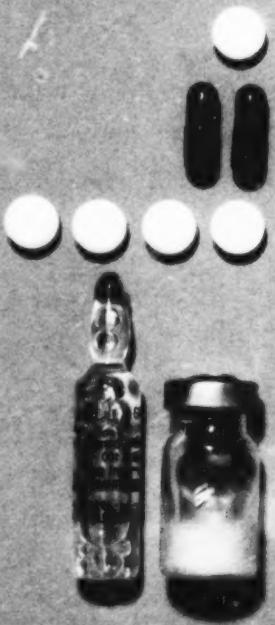
In China we have seen how poorly managed and inadequately funded TB programmes can have a disastrous effect. If patients are not monitored properly, many are not cured and consequently become chronic carriers of drug-resistant strains of the disease. The revised policies for registration and treatment monitoring have proved successful in making a high proportion of patients non-infectious within a short space of time. Even more important is the fact that we have been able to stop the development of chronic cases.

We hope that China – which has one-fifth of the world population – may help other countries, particularly in Asia, to undertake effective control measures against tuberculosis by adopting the same principles as this project. ■

Professor Yin Dakui is Vice Minister of Public Health of the People's Republic of China; the address of the Ministry of Public Health is: 44 Hou Hai Bei Yan, Beijing, China.

Daily regimen of chemotherapy for a TB patient weighing more than 50 kg

Initial Phase Treatment (2 months)



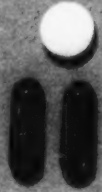
Isoniazid 300 mg

Rifampicin 300 mg (x2)

Pyrazinamide 500 mg (x4)

Streptomycin 1g (x1 injection)

Continuation phase (4 months)



Isoniazid 300 mg

Rifampicin 300 mg (x2)

One of the standard short-course TB chemotherapies recommended by WHO.

"Ten get it, nine die"

Kari Huus

When 67-year-old Zheng Xumin developed a stubborn cough last year, he thought he had a cold. So the retired professor from Beijing took a month-long beach vacation, during which he may have spread tuberculosis far and wide, because upon his return to the capital Zheng was diagnosed with the disease. Six months later he was cured – and that made him one of the lucky ones. TB still kills about 250 000 people a year in China, most of them peasants. In the Chinese countryside, they have a saying: "Ten get it, nine die."

The Chinese government in Beijing is working to prove the saying wrong. With technical guidance from WHO, close supervision, and a US\$ 55 million loan from the World Bank, the Ministry of Public Health has launched a programme aimed at halving the prevalence rate from the current 134 cases per 100 000 inhabitants by the year 2000. The "barefoot doctors" (rural health workers) are paid about US\$ 1 for each TB case they detect, and for each patient who successfully follows a full regimen of drug therapy they receive a \$10 bonus. The incentives are paying off: in the participating counties, as many TB cases were spotted in one quarter of 1992 as in all of 1991. Of those, 90% were cured.

Interruptions in treatment still appear to be the norm in many places not yet covered by the project: many TB sufferers quit taking costly drugs as soon as the symptoms disappear. In an impoverished mountain village 100 km south-west of Beijing, 32-year-old Wei Yidao has had TB since 1989. Sporadically he takes rifampicin. But it costs \$3.75 a bottle, and he can't afford it: Wei and his parents live on only \$240 a year. "He takes drugs for a while and he gets a little better," says the village doctor Zhang Shugui. "Then he stops." Meanwhile Wei is infecting others. His 62-year-old

mother contracted TB six months ago and her chances of survival seem slim.

Many cases in China escape the attention of medical workers. Hundreds of thousands of peasants move to the cities each year, many without the required residence permits. Some are afraid to get caught, so they won't register for TB treatment,

according to one Beijing physician; or they have no fixed residence, so it's difficult to supervise the treatment. The government's project has been a success so far in the provinces where it has been started. It has now to master the challenges of reaching all the counties, and especially the poorest where disease rates are often highest. ■

Kari Huus in Beijing wrote this article for the 17 May 1993 issue of Newsweek. It has been slightly adapted, with the kind permission of Newsweek.



Health workers cover a lot of ground to offer treatment and advice to people in their homes.

"The terrible chest"

Paul Nunn & Kraig Klaudt

Wilson Kwanyah doesn't remember much about the journey to Naamanga, in northern Tanzania. His father and friends had made a stretcher from thorn-tree branches and half carried and half dragged him into town. Yet he recalls with great clarity the nurse at the clinic explaining that he had *kifua kikuu*: the terrible chest.

Chen Li Ya, from Hunan Province in China, and Tom Smith, from London, have something in common with Wilson. They too have suffered from "the terrible chest", or tuberculosis as the doctors call it. Although from different continents, Chen Li, Tom and Wilson each learned that the terror of TB can be conquered.

Chen Li, from China

Chen Li comes from Cili county, a fertile, hilly area in northern Hunan, China. The village is a 15-minute walk from Chen Li's house, on a muddy path down the hill. It is a pleasant walk, as the path runs alongside a river where you can watch kingfishers snapping up the tiny fish that live by the edges of the stream. It takes almost 30 minutes to get back home again, up the hill; or 45 minutes for Chen Li when her chest was really bad.

Chen Li's problems with TB began 10 years earlier, when she started to cough. Since it was winter and almost everybody else over 40 years of age was coughing, she didn't pay much attention. Then her husband told her that she was getting thinner. In the evenings, even when it was cold, she often had a film of sweat on her forehead. When she coughed up a spoonful of bright red blood she finally went to see the village doctor. The blood frightened her, but it made it easy for the doctor to diagnose tuberculosis.



Receiving anti-TB drugs from a health worker in Cameroon.

In those days you had to pay for the TB medicines. With what amounted to almost all of his income, Chen Li's husband paid for the drugs. After a couple of months she felt better and was putting on weight again. But then the savings ran out. Rather than get into debt they both agreed that she would stop her treatment. The worst of the disease seemed to be over and, in any case, Chen Li hated all the injections which were given along with the other medicines.

But a few months later, Chen Li didn't feel so well. From time to time she coughed up blood or lay shivering in bed. But she survived, although she rarely went down to the village since it was such a struggle getting back home again. Then when her only grandson, who lived with them, started to cough and stopped gaining weight, Chen Li really began to worry.

About that time she heard on the people's radio that there was a new campaign in the county against TB. The government and provincial leaders had decided that TB was affecting too many people, so they had agreed with the World Bank and WHO to start a new treatment programme. Chen Li could hardly believe her ears when she heard that the treatment was free! She almost ran down the hill to see the village doctor.

When the doctor checked Chen Li's sputum, he confirmed that, sure enough, the TB bugs were still there. She was given one injection every other day (she shut her eyes when the needle went in) and different kinds of tablets that were fixed on a card wrapped in foil and plastic, one card for every other day. At first the village doctor even came up to the house every other day to bring the treatment. But soon he didn't have to. Chen Li could easily get down to his clinic and

back up the hill. Besides, she loved watching the kingfishers.

Best of all, the village doctor said that her grandson should also be tested. He was sent into town for an X-ray, and came back with the same kind of pills as Chen Li's, only fewer. Now he is almost fat!

Tom, from England

Tom Smith was of uncertain age and of no fixed abode; his address was "the streets of London". He never really settled anywhere and actually seemed happier in the *derries* (derelict buildings), where he and his mates would light a bonfire and drink anything they could lay their hands on. He was living this kind of existence when he first started coughing.

At first, Tom didn't know what to do about it. He had no doctor to go to. It was only when the police arrested him for being drunk and disorderly, and after he had coughed the whole night in the cells, that they called a doctor to see him. "TB", said the doctor, "come and see me in my surgery tomorrow". "Like hell", thought Tom, whose heart, mind and soul were set firmly on a drink as soon as he could get out of the police station. The police found him again though, and dragged him off to the doctor. And so his treatment started, and then stopped when he went off on a drinking binge, and started again when the police or the social worker caught up with him. And so on, for nearly ten years.

Whether from fatigue, or some vague sense of the danger he represented to others, or the simple desire for a warm bed in the middle of winter, Tom finally agreed to stay in the hospital for eight months to complete his treatment. By then, his TB was the dangerous, drug-resistant kind, brought on by all the interruptions in his treatment.

However, complete abstinence from the "demon drink" seemed too much to ask of Tom as part of his hospital admission. "Drink was always my problem", he would say. So at least once every weekend, one

or more of the off-duty medical officers would take him down to the pub and set him up with a glass of stout, or two.

It worked. Within about 3 months his sputum smears became negative, and a month later, the cultures too. He never had TB again, and was discharged into an old people's home. When last heard of, he was making contact with his family for the first time in 30 years.

Wilson, from Tanzania

Wilson Kwanyah became worried when his fever wouldn't go away. The local healer said it was because his wife's uncle had put a curse on him. They had had a disagreement several years earlier about a piece of land, and it was never properly settled. But the uncle had gone off to Dar es Salaam and that seemed to be the end of it until a few months previously when the uncle had returned, very thin, coughing and with diarrhoea. He didn't live long. They buried him with his ancestors. Then the rumours of this strange new disease, *ukimwi* or AIDS, started. The stories came first from Dar es Salaam and then from Nairobi.

Young people were dying, they said, with fever, cough and diarrhoea, and the doctors could do nothing.

Wilson's illness grew worse – with fever and a cough. He refused to go to the doctor, terrified he too had *ukimwi*. His wife, Teresita, sent for his father, a clinical officer in Bugoma. His father took one look at Wilson and said, "I don't know if this is TB, or *ukimwi* and TB. But whether it is *ukimwi* or not, TB is a danger to everybody in this house". He took some of Wilson's sputum into Naamanga to have it checked. It was TB. Wilson agreed to go for treatment. So Wilson, with the help of his father and friends, made the day-long journey to the clinic in Naamanga. The health workers gave him an injection, some capsules and some tablets every day. The fever departed within a week, and the cough soon after. After 2 months the nurse in the clinic checked his sputum again and it was clear. She said he could go home, but he had to come every month for the next 6 months to pick up his tablets, and he had to remember to swallow them every day, *bila ku'osa* – without fail! Once Wilson couldn't get into town because of the rains. Two days later, the district TB officer came by in the Ministry's Landrover and dropped off the tablets.

Wilson and Teresita still don't know for sure whether Wilson has the virus that causes *ukimwi*. But it seems to them that since he now feels entirely well, it's not very likely.

Chen Li, Tom and Wilson each showed great personal courage in seeking and finally sticking to a course of treatment. They probably would never have done so if it weren't for friends, relatives or spouses who supported them. They certainly couldn't have, if the treatment had not been free.

The drugs used in each of their cases were similar, although Tom needed a few extra ones. The way in which the drugs are provided is important – blister packs are thought to be a major factor in the success of the programme in China. The diagnosis is made in much the same

way the world over. While the kinds of supervision of treatment should vary with the needs of society, supervision of some kind is an essential part of good TB management. Every TB case is a potential threat to relatives, friends and acquaintances. But, as in Chen Li's case, being diagnosed oneself can also lead to the prevention of serious disease in close relatives. The connection between TB and AIDS or HIV is a real problem. But TB, even when associated with AIDS, is curable with proper treatment. Even in those sick with AIDS, TB should be treated to prevent its spread to others. ■

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TB demands a global effort now

The world cannot afford to wait. TB is on the rise again, in part because the disease has been neglected by national and international health programmes. Although the greatest number of TB cases are concentrated in Africa, Asia and Latin America, TB cannot be contained by political boundaries or more strict border controls.

Today's world is increasingly interdependent. With fast and accessible travel, migration, and immigration, infectious diseases like TB will not be stopped by borders. Over the long term, only a worldwide, systematic approach can solve this problem. In short, it will be impossible to control tuberculosis in the industrialized nations unless it is sharply reduced as a health threat in Africa, Asia and Latin America.

A price worth paying

José-Luis Bobadilla & Dean T. Jamison

Tuberculosis is among the most cost-effective diseases to control in adults over the age of 15 years, according to the World development report 1993: investing in health. For a relatively small amount of money, nearly 15 million deaths could be prevented in the next 10 years.



Examining a TB-infected child in Nepal. The world community is mobilizing to control the preventable scourge.

October 1977: WHO vaccination teams descended on Merca, Somalia, to protect the city from smallpox after a single case was found there. Smallpox had been killing nearly two million people each year until WHO began a global effort to eradicate the disease. Fortunately, the Merca case was the world's last recorded incident of endemic smallpox.

October 1982: Investigators descended on Chicago, USA, to protect the city following a series of malicious deaths caused by pain relievers being laced with cyanide. The poisoned capsules had killed seven people and the resulting panic was causing many people to avoid pain relief medicine. Fortunately, the investigators discovered no other tampered drugs.

These two health emergencies had comparable price tags; US\$ 300 million was spent over ten years to

eradicate the smallpox virus, and \$100 million was spent in the space of a few months to ensure that there were no further cyanide poisonings. Yet the results were very different. Tens of millions of lives are estimated to have been saved by the intensified smallpox eradication programme. It is debatable how many – if any – lives were saved by the effort to prevent the poisoning of consumers by over-the-counter pain relievers.

As public health budgets become more stretched, it is becoming increasingly necessary to make comparisons such as these to determine which health interventions provide the best value for money. With so many pressing public health needs, it is more and more difficult to argue that "no cost is too great to pay to save one human life."

This is not to say that the issue does not raise a number of difficult questions. For example, how can one compare health care costs in Merca with those in Chicago? How can disabling diseases be compared with terminal diseases? Is extending an elderly person's life by 10 years equivalent to extending a child's life by 60 years?

WHO and the World Bank have been wrestling with issues such as these in preparing a background document on the burden of disease for the *World development report 1993: investing in health*, published by the World Bank this July. In view of limited public health spending and a limitless number of preventable deaths and illnesses in the world, the report attempts to determine which diseases justify the most urgent attention.

The report has devised a common standard, known as a "disability-adjusted life year," or DALY, to help make health care comparisons. As explained in the March-April issue of *World Health*, a DALY measures the number of healthy years of life lost through premature death, or alternatively, the number of healthy years of life gained by one person when that person is cured or able to avoid a disease. It also measures the healthy years of life lost due to disability resulting from a disease. For example, blindness in a 25-year-old would result in a greater number of lost healthy years of life than would the death of an 80-year-old.

To assess cost-effectiveness, the costs of preventing or treating a disease are related to the number of healthy years of life gained by that intervention. The formula is more complex for some diseases, since treating an infectious disease may also have benefits in preventing further infections. For example, when an infectious TB patient is treated, this also prevents the infection of dozens of other people.

One of the findings of the *World development report* is that tuberculosis is among the most cost-effective diseases to control in adults over the age of 15 years. This supports what research experts have been saying recently – that for a relatively small amount of money, nearly 15 million deaths from TB could be prevented in the next 10 years.

Studies in Malawi, Mozambique and the United Republic of Tanzania show that, if the additional TB cases prevented by treating an infectious patient are considered, the cost is as low as \$20 and never more than \$100 for every life saved. This translates into as little as 90 cents for each year of life saved.

WHO has found that short-course chemotherapy greatly increases the cost-effectiveness of control programmes. Programmes that hospitalize patients to improve treatment compliance, or those which still use 12-month treatment, are also cost-effective, though clearly not as cost-effective as the six-month treatment recommended by WHO (see page 25).

The *World development report* concludes that too much public health money – as much as 40% – is spent on health interventions with low cost-effectiveness, such as heart surgery, surgery for most cancers and intensive care for severely premature babies, while critical and highly cost-effective interventions, such as the treatment of tuberculosis, remain under-funded. The report argues that, by increasing funding for highly cost-effective health interventions, millions of lives and billions of dollars could be saved. Short-course chemotherapy for TB control should, therefore, according to the report, be included with the clinical services provided by countries.

History has a way of repeating itself, and it is to be hoped that the world learns each time. In 1982, \$100 million was mobilized to deal with a local cyanide poisoning incident at a time when funding to address the emerging AIDS epidemic was virtually nonexistent. Large numbers of people became infected with HIV because society was slow to recognize that HIV posed a far greater threat to its health than did one deranged person in Chicago. A decade later, projects of marginal benefit continue to attract huge sums of money, while TB programmes go neglected and multidrug-resistant strains of TB are gaining a foothold in every continent. ■

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Chemicals are important for human activities, but they may become a threat for people's health. The September-October issue of *World Health* will look at different aspects of Chemical Safety, including safe disposal of toxic wastes and effects of chemicals on the climate. ■

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THE MAJOR THRUST OF TB PROGRAMMES
MUST BE TO CURE ADULTS WITH
INFECTIOUS TUBERCULOSIS AND THEREBY
STOP ITS TRANSMISSION IN THE COMMUNITY

